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ORIGINAL ARTICLE

Interleukin-27 and its relation to disease parameters in SLE patients

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KEYWORDS

Interleukin-27;
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Abstract *Introduction:* IL-27 exerts profound anti-inflammatory effects in several experimental autoimmune models, suggesting that it may be therapeutically relevant in SLE.

Aim of the work: To evaluate IL-27 level in SLE patients and its association to clinical manifestations, disease activity parameters and management strategy.

Patients and methods: We studied 80 SLE patients and 50 controls in a cross sectional study. Demographic, clinical and serological data were evaluated. Systemic lupus erythematosus disease activity index (SLEDAI) and Systemic Lupus International Collaboration Clinics/ACR damage index (SLICC) were assessed. Serum IL-27 was measured by ELISA.

Results: There was statistically significant difference in IL-27 level in SLE patients and healthy controls (9.7 ± 21.9 pg/ml vs 20.2 ± 47.3 pg/ml in SLE vs controls, respectively) ($p = 0.04$), also it was found that IL-27 level was statistically significantly lower in SLE patients with lupus nephritis ($p = 0.02$) and cerebritis ($p = 0.03$). Interleukin 27 level had a statistically significant negative correlation with the cumulative dose of hydroxychloroquine and azathioprine ($r = -0.3$, $p = 0.03$ and $r = -0.3$ and $p = 0.04$, respectively).

Conclusion: IL-27 has anti-inflammatory effect in SLE patients especially those without nephritis or cerebritis and can be therapeutically relevant in SLE. To confirm our results we propose larger scale, multicentre studies with longer evaluation periods.

1. Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by the production of many autoantibodies, complement activation, and immune-complex deposition, causing tissue and organ injury. The pathogenetic mechanisms of SLE are still unclear. Many mechanisms could contribute to this disease. Activated autoreactive T helper (Th) cells have been shown to be implicated in the pathogenesis of SLE, which

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help B cells to differentiate and produce pathogenic autoantibodies [1].

1.1. IL-27 is one of IL-12 cytokine family affecting T cells

Interleukin 27 was identified to be related to the IL-12 cytokine family. These family members play important roles in the regulation of Th cell differentiation. It has been found that IL-27 is also involved in the regulation of Th17 responses, suppressing Th17 differentiation and IL-17 production [2]. In this context, IL-27 has an immunosuppressive feature as anti-inflammatory effects of IL-27 have also been demonstrated in various experimental settings. Thus, IL-27 seems to have two distinct functions in immune responses: one as an initiator of Th1-type immune responses and the other as an attenuator of immune/inflammatory responses [3].

IL-12, a heterodimeric cytokine composed of two subunits, p35 and p40, is critical in Th1 differentiation [4]. Also IL-23 and IL-27 were identified as heterodimeric cytokines functionally and structurally related to IL-12 [5]. In addition, IL-35 was identified as a new IL-12 family member which is composed of Epstein-Barr-induced molecule 3 (EBI-3) and p35 [6].

IL-23 is composed of the p40 subunit of IL-12 and p19, but IL-27 is composed of EBI-3, a p40-related molecule, a p28 and a p35-related molecule [7].

IL-12R is composed of two subunits: β1 and β2. Downstream of IL-12R, STAT4 is activated for direct induction of the IFN-γ gene. IL-23R uses unique IL-23R subunits and shares IL-12R β 1 subunits. IL-27R is made with WSX-1 (also called the IL-27Rα chain or T cell cytokine receptor) and gp130, the signal transducing subunit of the IL-6R complex. Downstream of IL-27R, STAT1 and STAT3 are activated by ligand binding, IL-35R has not been identified yet [8].

IL-27 enhances cytotoxic activity against tumors of CD8+ T cells. IL-27R signaling is critical in STAT1 and T-bet-induced IFN-γ production by CD8+ T cells [9]. Hisada et al. [10] reported that C26 cells engineered to produce IL-27 conferred protective immunity in a CD8+ T cells and IFN-γ-dependent manner when inoculated in immuno-competent mice. The effect was also dependent on T-bet activation. IL-27 produced by tumor cells also enhanced IFN-γ production by NK cells. STAT1- and T-bet-dependent augmentation of IL-12Rβ2, granzyme B, and perforin expression in CD8+ T cells by tumor derived IL-27 was observed *in vitro* [11].

1.2. Effects of IL-27 on other types of cells

IL-27 also has an impact on B cell differentiation and Ig production. IL-27 induced proliferation of activated naive B cells but not memory B cells, indicating that IL-27 exerts differential effects on B cells depending on activation/differentiation status of the cells [12]. IL-27 stimulation of mouse B cells induced STAT1 activation and T-bet expression followed by class-switching of B cells to IgG2a (Th1-dependent Ig subtype) producing cells In contrast, IL-27 inhibited IgG1 (Th2-dependent Ig subtype) class-switching. Interestingly, IL-27 up regulates IL-4 induced IgE production by naive B cells without affecting Cε promoter activity. STAT1 and T-bet-dependent activation of B cells and Th1-related Ig production are also reminiscent of the effects of IL-27 on naive CD4+ T cells. [13].

IL-27 augments NK cell activity although the enhancement of IFN-γ production in NK cells by the inoculation of IL-27-producing tumor cells was reported [14], Oniki et al. [15] reported IFN-γ-independent enhancement of NK cell-mediated anti-tumor immunity by IL-27.

Effects of IL-27 on macrophage/monocyte are complicated too. It was reported that IL-27-mediated augmentation of MHC class I/II expression as well as transporter associated with antigen processing 1 and β2-microglobin expression in a THP-1 human monocyte cell line [16]. Expression of costimulatory molecules CD80 and CD86 and an adhesion molecule CD54 was also augmented by IL-27. Thus, IL-27 may enhance immune responses by the induction of genes involved in antigen presenting activity of THP-1 cells. IL-27-stimulated monocytes showed enhanced TLR responsiveness and produced more IL-6 and TNF-α as compared with cells without IL-27 stimulation [3].

Caroline Diveu et al. [17] reported that, IL 27R-deficient mice infected with *Toxoplasma gondii*, an encephalitis model, developed severe neuroinflammation associated with exaggerated T cell responses and overproduction of IFN-γ and TNF-α during the acute phase of the disease; mortality was high due to uncontrolled immune pathology [18]. Additionally, an increased frequency of Th17 cells was found in the brains of *Toxoplasma*-infected IL-27R-deficient mice during the chronic phase of infection [19]. The IL-27R-deficient mice are also hyper susceptible to experimental autoimmune encephalomyelitis (EAE) and more Th17 cells were generated in these mice as well [20]. These two reports stress that IL-27 negatively regulates the development of Th17 cells in vivo. It is important to point out that these studies are based on the assumption that IL-27R is the only receptor for IL-27. Similar studies in IL-27p28 or IL-27 EBI3-deficient mice have not yet been performed to confirm this assumption [17].

Since it has been demonstrated that IL-27 has two conflicting properties: pro-inflammatory and anti-inflammatory, therefore in the present study we investigated the serum IL-27 level in SLE patients and its relation to various disease parameters and treatment strategy.

2. Patients and methods

2.1. Patients

Eighty SLE patients were recruited consecutively, 97.5% of them are females and 2.5% are males fulfilling the updated American College of Rheumatology (ACR) revised criteria for the classification of SLE [21] were consecutively recruited from Rheumatology Department, Cairo University Hospitals. Full history taking, thorough clinical examination and laboratory investigations were done. Assessment of disease activity was done using the Systemic lupus erythematosus disease activity index (SLEDAI) [22], disease damage using the Systemic Lupus International Collaboration Clinics/ACR damage index (SLICC/DI) [23]. Secondary APS was diagnosed according to the Sapporo criteria [24]. Informed consents were taken from the patients and the study was approved by the local ethics committee.

2.2. Renal biopsy

The kidney biopsy was performed in all patients who had either proteinuria (urinary protein concentration ⩾ 500 mg/

dl), abnormal urinary sediment, or an elevated serum creatinine level. The biopsy specimens had been studied, using light and immunofluorescence microscopy, by renal pathologists who had no knowledge of the clinical and laboratory features of the patients. The World Health Organization (WHO) classification of lupus glomerulonephritis [25] and the WHO activity and chronicity index scores [26] were evaluated.

2.3. Laboratory investigations

Blood was drawn at the time of the study for analyses which included the following: antiphospholipid antibodies (aPL) (positive if IgG or IgM ACL was >40 IU/ml or if the lupus anticoagulants (“LAC”) was present). Antinuclear antibody testing (ANA), anti-DNA using indirect immunofluorescence, C-reactive protein (CRP), serum complement (C3 and C4) levels by nephelometry and glomerular filtration rate were done to all patients. A complete blood picture, lipid profile, serum creatinine, fasting blood sugar and liver functions were tested for all enrolled cases.

Human IL-27 in serum was measured by sandwich enzyme-linked immunosorbent assay; reagents were supplied by Ray-Bio [27] and according to the manufacturer’s recommendation. Briefly, 96-well plates coated with biotinylated IL-27 were incubated with 100-KL sera for 120 min at 37-°C. Then, the plates were washed 6 times with the wash solutions of the kits. Biotinylated abs of 100 KL was pipetted into each of the microplate wells and incubated for 60 min at room temperature. After 6 washes, 100 KL of enzyme conjugate was added and incubated for 30 min at 37-°C and then washed as before. A 100-KL tetramethyl benzidine solution was added and incubated for 15 min in the dark. Color release was stopped with the addition of 100 KL of stop solution. The microplate wells were read at 450-nm reference filter within 30 min, and the optical density value of each well was recorded. Then, the concentrations were calculated according to the optical density values, and the results were expressed as picograms per milliliter (intraassay: coefficient of variation, G10%; interassay: coefficient of variation, G15%) [28].

Statistics: Statistical analysis, Statistical Package for Social Science program, version 15, was used for analysis of data. Data were presented as number (percent) and mean ± SD. Mann–Whitney test was used for the analysis of two quantitative data. Spearman correlation was used for detection of the relation between two variables. *P* value was considered significant if <0.05 [29] .

3. Results

3.1. Data of all studied SLE patients

Eighty SLE patients (78 females and 2 males) (39:1 female/male, respectively) were examined during this study with a mean age of 29.3 ± 9.8 years and a mean disease duration of 5.6 ± 4.7 years (as shown in Table 1) as well as 50 controls (49 females and one male) matched for age and sex, as their mean age was 27.6 ± 10.4 years. All patients were taking steroids (dose ranged from 15 to 45 mg/day), all patients were on hydroxychloroquine (dose ranged from 200 to 400 mg/day), 74 patients on azathioprine (dose ranged from 100 to 150 mg/day) and 44 patients were receiving monthly cyclophosphamide pulse therapy depending on extent of renal lesion (dose ranged from 600 to 1000 mg (as shown in Table 2).

Table 1 Descriptive data of the studied SLE patients and its correlation to IL 27 level.

Characteristics	Value *n* (%), mean ± SD
Duration (years)	5.6 ± 4.6
Age (mean ± SD)	29.3 ± 9.8
Nephritis (No. (%))	64/80 (80%)
○ Class II	12/64 (18.8%)
○ Class III	15/64 (23.4%)
○ Class IV	30/64 (46.9%)
○ Class V	4/64 (6.3%)
○ Class II–V	3/64 (4.7%)
► Active nephritis	40/64 (62.5%)
► Chronic nephritis	24/64 (37.5%)
Neuropsychiatric manifestations	28/80 (35%)
Psychosis (No. (%))	18/80 (22.5%)
Seizure (No. (%))	7/80 (22.5%)
Lupus headache (No. (%))	3/80 (3.8%)
Mucocutaneous manifestations (No. (%))	69/80 (86.3%)
Serositis (No. (%))	64/80 (80%)
Arthritis (No. (%))	37/80 (46.3%)
BMI (kg/m^2) (mean ± SD)	25.9 ± 6.5
SLEDAI score (mean ± SD)	17.3 ± 8.5
SLICC (mean ± SD)	0.6 ± 0.9
Hypertension (No. (%))	36/80 (45%)
Diabetes mellitus (No. (%))	6/80 (7.5%)
Laboratory data	
IL-27(pg/ml) (mean ± SD)	9.7 ± 21.9
HGB (g/dl) (mean ± SD)	10.7 ± 1.3
TLC (10^3/mm^3) (mean ± SD)	4.5 ± 1.3
Platelets (10^3/mm^3) (mean ± SD)	150.7 ± 30.5
GFR(ml/min) (mean ± SD)	70.4 ± 21.3
Cholesterol (mg/dl) (mean ± SD)	168.7 ± 60.4
Triglycerides (mg/dl) (mean ± SD)	155.2 ± 73.1
HDL (mg/dl) (mean ± SD)	49.3 ± 15.6
LDL (mg/dl) (mean ± SD)	175.2 ± 39.1
ALT (U/L) (mean ± SD)	20.4 ± 7.2
AST (U/L) (mean ± SD)	18.9 ± 9.8
FBS (mg/dl) (mean ± SD)	93.1 ± 17.9
ACL positive (No. (%))	18/80 (22.5%)
LAC positive (No. (%))	14/80 (17.5%)
Creatinine (mg/dl) (mean ± SD)	0.8 ± 0.4
C3 (mg/dl) (mean ± SD)	80 ± 37
C4 (mg/dl) (mean ± SD)	17.1 ± 7.2
CRP (mg/dl) (mean ± SD)	3.7 ± 11.8

BMI: body mass index, SLEDAI: Systemic lupus erythematosus disease activity index, SLICC: Systemic Lupus International Collaboration Clinics/ACR damage index, IL-27: Interleukin 27, HGB: hemoglobin, TLC: total leukocyte count, GFR: glomerular filtration rate, HDL: high density lipoprotein, LDL: low density lipoprotein, ALT: alanine transferase, AST: aspartame transferase, FBS: fasting blood sugar, ACL: anticardiolipin antibody, LAC: lupus anticoagulant,C3:complement 3, C4: complement 4, CRP: C-reactive protein.

3.2. IL-27 in SLE patients and control group

Interleukin-27 level in SLE patients was statistically significantly lower than in the control group with mean ± SD of

Table 2 Medications used in the studied group.

Current medications	Mean ± S.D.
Steroid cumulative dose (g) (mean ± SD)	1.1 ± 0.6
HQN cumulative dose (g) (mean ± SD)	17.1 ± 11.4
Azathioprine cumulative dose (g) (mean ± SD)	3.6 ± 3
CYC cumulative dose (g) (mean ± SD)	3.8 ± 3.8

HQN: hydroxychloroqiune, CyC: cyclophosphamide.

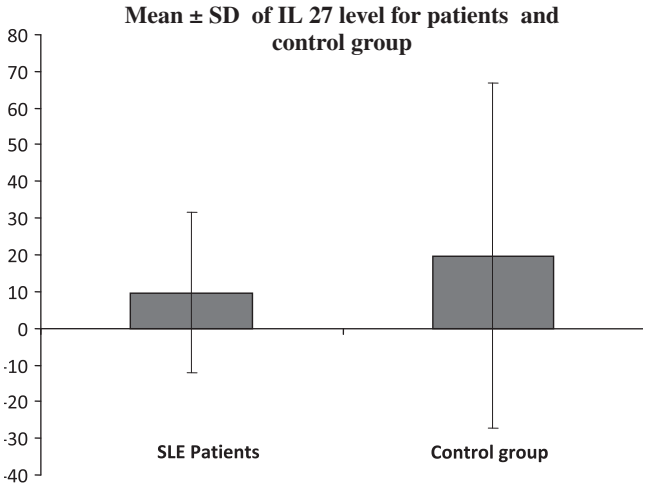


Figure 1 IL-27 in SLE patients and control group.

(9.7 ± 21.9 pg/ml vs 20.2 ± 47.3 pg/ml, respectively) (p = 0.04) as (shown in Fig. 1).

3.3. IL-27 in SLE patients and its relation to all clinical and laboratory parameters

On correlating IL-27 level to all clinical and laboratory parameters, a significant negative correlation was found with psychosis and nephritis (p = 0.04 and p = 0.03, respectively, r = −0.2, and r = −0.3, respectively). But there was no significant correlation with other clinical manifestations or laboratory parameters (as shown in Table 3).

3.4. IL-27 in SLE with renal and neuropsychiatric manifestations

On comparing SLE patients with and without nephritis it was found that, IL-27 level was significantly lower in patients with nephritis (p = 0.02). Also it was found that, the level of IL-27 was significantly lower in patients with cerebritis (p = 0.03) (as shown in Table 4).

3.5. Relation of IL-27 to disease activity measures and damage index

On correlating the level of IL-27 and disease activity score, it was found that IL-27 had no statistically significant correlation with SLEDAI score (r = −0.3 and p = 0.06), or damage index SLICC score (r = −0.1 and p = 0.5) (as shown in Table 5).

Table 3 IL-27 and its correlation to clinical and laboratory parameters.

Characteristics	Value n (%), mean ± SD	*P* value
Duration (years)	5.6 ± 4.6	0.2
Age mean	29.3 ± 9.8	0.9
Nephritis	64/80 (80%)	0.03*
Psychosis	18/80 (22.5%)	0.04*
Seizure	7/80 (22.5%)	0.06
Lupus headache	3/80 (3.8%)	0.07
Mucocutaneous manifestaions	69/80 (86.3%)	0.7
Serositis	64/80 (80%)	0.8
Arthritis	37/80 (46.3%)	0.6
BMI (kg/m^2)	25.9 ± 6.5	0.4
Hypertension	36/80 (45%)	0.09
Diabetes mellitus	6/80 (7.5%)	0.9
Laboratory data		
IL-27(pg/ml)	9.7 ± 21.9	
HGB (g/dl)	10.7 ± 1.3	0.3
TLC (10^3/mm^3)	4.5 ± 1.3	0.4
Platelets (10^3/mm^3)	150.7 ± 30.5	0.2
GFR (ml/min)	70.4 ± 21.3	0.06
Cholesterol (mg/dl)	168.7 ± 60.4	0.4
Triglycerides (mg/dl)	155.2 ± 73.1	0.6
HDL (mg/dl)	49.3 ± 15.6	0.5
LDL (mg/dl)	175.2 ± 39.1	0.9
ALT (U/L)	20.4 ± 7.2	0.7
AST (U/L)	18.9 ± 9.8	0.6
FBS (mg/dl)	93.1 ± 17.9	0.1
ACL positive	18/80 (22.5%)	0.5
LAC positive	14/80 (17.5%)	0.4
Creatinine (mg/dl)	0.8 ± 0.4	0.07
C3 (mg/dl)	80 ± 37	0.3
C4 (mg/dl)	17.1 ± 7.2	0.6
CRP (mg/dl)	3.7 ± 11.8	0.08

BMI: body mass index, IL-27: Interleukin 27, HGB: hemoglobin, TLC: total leukocyte count, GFR: glomerular filtration rate, HDL: high density lipoprotein, LDL: low density lipoprotein, ALT: alanine transferase, AST: aspartame transferase, FBS: fasting blood sugar, ACL: anticardiolipin antibody, LAC: lupus anticoagulant, C3: complement 3, C4: complement 4, CRP: C-reactive protein.
* Statistically significant value (p < 0.05).

Table 4 IL-27 in SLE patients with nephritis and cerebritis.

SLE patients	IL-27 level (mean ± S.D)	*P* value
Nephritis		0.02*
Yes	1 ± 1.1	
No	11.7 ± 27.5	
Cerebritis		0.03*
Yes	2 ± 0.9	
No	11.9 ± 24.5	

* Statistically significant value (p < 0.05).

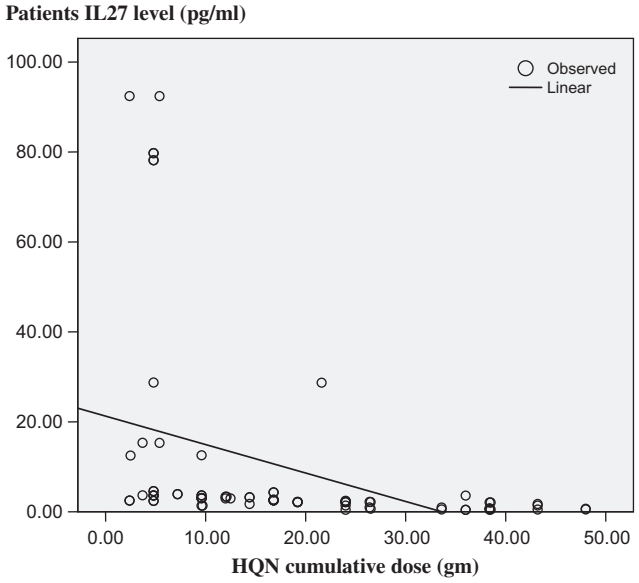
3.6. Il-27 and its relation to the received medications

Interleukin 27 level had a statistically significant negative correlation with the cumulative dose of hydroxychloroquine and azathioprine (r = −0.3, p = 0.03 and r = −0.3 and p = 0.04, respectively) (as shown in Table 5) and (Graphs 1 and 2).

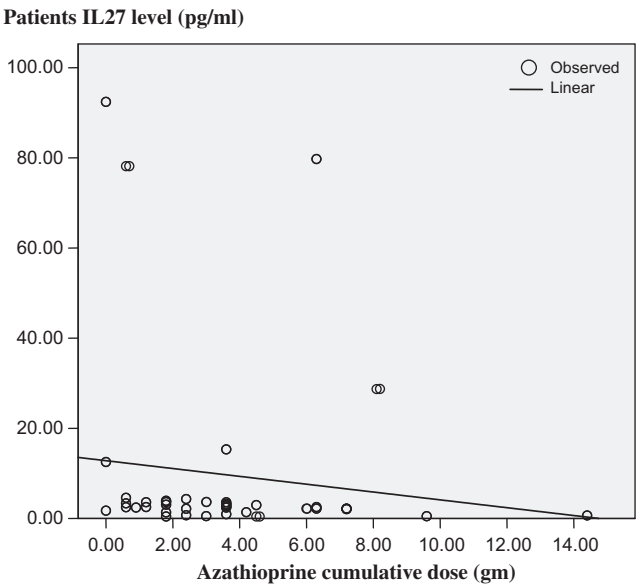
Table 5 IL-27 and relation to the disease activity and damage indices and medications used in the studied group.

Disease activity and damage index	Mean ± S.D	*P* value
SLEDAI score	17.3 ± 8.5	0.06
SLICC	0.6 ± 0.9	0.5
Current medications		
Steroid cumulative dose (g)	1.1 ± 0.6	0.1
HQN cumulative dose (g)	17.1 ± 11.4	0.03*
Azathioprine cumulative dose (g)	3.6 ± 3	0.04*
CYC cumulative dose (g)	3.8 ± 3.8	0.5

SLEDAI: Systemic lupus erythematosus disease activity index, SLICC: Systemic Lupus International Collaboration Clinics/ACR damage index, HQN: hydroxychloroquine, CyC: cyclophosphamide.
* Statistically significant value ($p < 0.05$).



Graph 1 Il-27 and its relation to hydroxychloroquine cumulative dose.



Graph 2 Il-27 and its relation to azathioprine cumulative dose.

4. Discussion

In the present study we found that interleukin-27 level in SLE patients was statistically significantly lower than that in the control group ($p = 0.04$), this coincides with the results of Li et al. [28], who examined Fifty-six patients with SLE and 30 healthy volunteers were recruited. Serum IL-27 levels were detected by enzyme-linked immunosorbent assay. The clinical and laboratory parameters were collected from medical records or by questionnaire. The serum IL-27 level in SLE patients was significantly lower than that in healthy controls ($P < 0.001$).

This can be explained as interleukin-27 is being consumed in several experimental autoimmune models. As its presence had suppressive effects on T(h)17 cells, which are implicated in the pathogenesis of SLE. Moreover, administration of IL-27 or augmentation of IL-27 signaling suppresses some autoimmune diseases, including autoimmune diabetes and murine lupus, suggesting that IL-27 may be therapeutically relevant in SLE [30].

Li et al. [28] reported that, compared to SLE patients without nephritis, patients with nephritis had a significantly decreased serum IL-27 level ($P < 0.05$) and this coincides with the results in the present study, as we found that, IL-27 level was significantly lower in patients with nephritis ($p = 0.02$) in comparison to patients without nephritis.

This can be explained partially with the results of Yu and Gaffen [31] who considered that IL-17 can promote the recruitment of inflammatory cells to target organs such as kidney. Where as Th17 differentiation and IL-17 production could be suppressed by IL-27.

In the current study, there was no statistically significant correlation with SLEDAI score ($p = 0.06$), or damage index SLICC score ($p = 0.5$). This coincides with the results of Li et al. [28] who found no significant difference between less active and more active SLE patients ($P > 0.05$).

On reviewing all the available literature, there were no available data on the association of IL-27 and cerebritis except in murine models, in the current study, we found that the level of IL-27 was significantly lower in patients with cerebritis and this can be explained by the results of Stumhofer et al. [19], who reported that, many studies had focused on the events that influence the development of interleukin 17 (IL-17)-producing T helper cells (T_H-17 cells) associated with autoimmunity, such as experimental autoimmune encephalitis (EAE), but relatively little is known about the cytokines that antagonize T_H-17 cell effector responses. So Stumhofer et al. [19] showed that IL-27 receptor-deficient mice chronically infected with *Toxoplasma gondii* developed severe neuro-inflammation that was $CD4^+$ T cell dependent and was associated with a prominent IL-17 response. *In vitro*, treatment of naive primary T cells with IL-27 suppressed the development T_H-17 cells induced by IL-6 and transforming growth factor-β, which was dependent on the intracellular signaling molecule STAT1 but was independent of inhibition of IL-6 signaling mediated by

the suppressor protein SOCS3. Thus IL-27, a potent inhibitor of T_H-17 cell development, may be a useful target for treating inflammatory diseases mediated by these cells.

In the present study, it was found that IL-27 had statistically significant negative correlation with the cumulative dose of hydroxychloroqiune and azathioprine ($p = 0.03$ and $p = 0.04$, respectively), and this could be explained as in active SLE, patients need higher doses of medications for longer duration than quiescent patients and this also proves that organ inflammation in SLE patients as nephritis and cerebritis show low level of IL27 which may be consumed in inflammation. But there was no available studies commenting on the relation of IL27 to the medications received as they studied patients before taking any medications, but studies recommended the use of IL-27 antagonists in conjunction with other standard therapies for lupus, such as immunosuppressive drugs (e.g., methotrexate, azathioprine, cyclophosphamide, chlorambucil, mycophenolate mofetil, cyclosporine, hydroxychloroqiune and the like) [32].

Conclusion: Interleukin-27 exerts profound anti-inflammatory effects in SLE patients proved by the lower serum level of IL-27 in SLE patients with nephritis and cerebritis than those without. This suggests that IL-27 may be therapeutically relevant in SLE. Also it was found that IL27 had a negative correlation with the cumulative dose of HQN and azathioprine.

Conflict of Interest

No conflict of interest.

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